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ATHEROSCLEROSIS (CERTAIN PROBLEMS OF PATHOGENESIS, PROPHYLAXIS, AND TREATMENT)

[This is a translation of an article written by Prof. P. Ye. Lukomskiy in Sovetskaya Meditsina (Soviet Medicine), Vol. 23, No. 12, Moscow, 1959, pages 8-25.]

The basic premises of the theory of origin of atherosclerosis formulated by N. N. Anichkov received recognition not only in the Soviet Union but also abroad. Of great significance to the formulation of this theory was the construction of an experimental model of atherosclerosis in rabbits. It is true that the initial experiments for inducing atherosclerosis in rabbits by feeding them egg yolks or chicken eggs (A. I. Ignatovskiyy, 1908; L. M. Starokadomskiy, 1909) were not at first interpreted correctly: the development of atherosclerosis of the aorta was linked with the fact that the experimental animals were fed large quantitites of animal proteins. However, very soon afterwards one began to attach decisive importance to fats for the origin of experimental atherosclerosis and, finally, to cholesterin. (N. V. Sukkey, 1910; N. V. Veselkin, 1912).

The ability to induce experimental atherosclerosis by feeding cholesterin to rabbits (N. N. Anichkov and S. S. Khalatov, 1913) was the deciding factor in the creation of the cholesterin infiltration theory of atherosclerosis. Subsequently, one succeeded in inducing atherosclerosis in chickens, dogs, monkeys, and other animals by feeding them cholesterin. It is true that in some cases it was necessary to resort to additional measures, such as the reduction of the function of the thyroid in dogs with methylthiouracil (Steiner, Kendall, 1946, and a number of other American authors; T. A. Sinitsyna, 1956; V. N. Mentova and Z. T. Semoylova, 1959),of, in the case of monkeys, limiting the amount of sulfur-containing amino acids in food rich in

cholesterin (Mann, 1953).

The theory of the pathogenesis of atherosclerosis, as developed by N. N. Anichkov and his school, is so well known that it needs no detailed exposition. We shall mention only some basic theses of this theory. Anichkov considers atherosclerosis to be an impairment of metabolism, primarily, of lipoids. As a result of an impaired lipoid metabolism, an accumulation of cholesterin in the intima of the arteries takes place, chiefly in the form of its esthers, and causes subsequent reactive morphological changes in the vascular walls, which leads to a pronounced atherosclerosis syndrome. It is important to remember that Anichkov proved the inadequacy of previous views of atherosclerosis as a primary inflammatory or degenerative process, or a disease connected with the wearing out of the blood vessels. At the same time Anichkov attaches certain significance to some additional, or contributory factors, among them - dystrophic changes in the blood vessels. He demonstrated that, upon intravenous administration of adrenalin to rabbits, fibrous platchets develop in their arteries. Feeding of cholesterol to these rabbits leads to the development of atherosclerosis in the area of vascular walls damaged by adrenalin. Anichkov attaches secondary importance to previous changes in the vessels in the development of atherosclerosis, stating that in a preponderant majority of cases of atherosclerosis the presence of these changes could not be demonstrated.

Recently some authors called attention to the impairment of the basic substance of the connective tissue of arterial walls as a factor which may contribute to the accumulation of lipoids and the development of atherosclerosis. Thus, Adlersberg and associates noted that in certain experiments a parallelism between the development of hypercholesterinemia and atherosclerosis is not evident. Under the effect of steroid hormones of the adrenal cortex and ACTH [adrenocorticosteroid hormone] in rabbits fed on cholesterin, hypercholesterinemia increases but the development of atherosclerosis is retarded. In contrast, administration of hyaluronidase inhibits the development of hypercholesterinemia and enhances the development of

atherosclerosis. The authors explain these facts as follows: under the effect of steroid hormones there is a reduction of the permeability of the capillaries of the vascular walls, while under the effect of hyaluronidase there is an impairment of the mucopolysaccharides of the basic substance of the connective tissue of the arterial walls. This fact served as a basis for Adlersberg and his associates to point out the importance of the tissue factor in atherogenesis. Recently, upon administering Vitamin K to rabbits who had been fed cholesterin, Samoylova observed an acceleration in the development of hypercholesterinemia and less marked atherosclerotic changes. In order to explain this fact she also refers to possible changes in the vascular walls.

The importance which is attached to the impairment of lipoid metabolism, in the pathogenesis of atherosclerosis, deposits of cholesterin and its esters in the intima of blood vessels, and the development of cholesterinemia in alimentary cholesterin atherosclerosis in animals, attracted the attention of researchers to the study of the metabolism of cholesterin, and , in particular, its content in the blood. Apparently it was Vogel (1847) who was the first to demonstrate the presence of cholesterin in atherosclerotically altered blood vessesl (according to Gertler and associates). Windaus (1908) found six times more cholesterin and 20 times more cholesterin esters in atherosclerotic than in normal aortas. Similar data were obtained by Grigaut in the Chauffard clinic. Subsequently, determination of the lipoid content in atherosclerotic aortas became the subject of numerous studies (Schönheimer, et al.) which basically confirmed the data of Windaus. Chauffard, in 1911, demonstrated in some atherosclerotic patients the presence of hypercholesterinemia which he considered as an indicator of the activity of the process. A. L. Myasnikov (1924) and B. V. Il'inskiy (1951), having found hypercholesterinemia in atherosclerotic patients, also came to the conclusion that it is observed in patients with an advanced stage of the disease. The cholesterin level of the blood was also the subject of many studies by American scientists.

A summary of a part of these works is given in the monograph by Katz and Stamler. Without dwelling on details, we must mention that the average level of cholesterin in patients with coronary atherosclerosis is higher than normal. However, in some individuals, atherosclerotic as well as healthy, the amplitude of fluctuations of the cholesterin level of the serum is very marked; therefore, the blood serum cholesterin indices of healthy and sick individuals overlap. In this respect, the data of Gertler, Garn, and Lerman are interesting. In 146 individuals of the control group the total serum cholesterin was on the average -- 224.4 mg percent, and in 97 patients with coronary atherosclerosis -- 286.5 mg percent. The quantity of serum cholesterin in healthy individuals varied between 148 and 332 mg percent, and in the sick -- 167 and 490 mg percent.

In recent years, in the studies of atherosclerosis in our clinic, the serum cholesterin was determined in 450 patients with coronary atherosclerosis who had no observable phenomena of insufficiency of blood circulation. We accepted as normal 150 to 180 mg percent of serum cholesterin (according to Grigo and Blur); however, even 200 mg percent of cholesterin was considered as borderline between normal and pathological. As seen from Table 1, in 195 out of 450 patients with coronary atherosclerosis, i.e., in 43.3 percent the cholesterin content did not exceed 200 mg percent; in 37 patients, i.e., in 8.2 percent, the content of cholesterin was below normal (from 122 to 150 mg percent). The mean content of cholesterin was 212 mg percent.

Thus, the results of our studies as well as the data in the literature show that a pronounced coronary atherosclerosis may proceed with normal or even somewhat reduced cholesterinemia. If in some cases it can be explained by the phasic character of the atherosclerotic process metnioned earlier, it nevertheless cannot be fully applied to the numerous cases of coronary atherosclerosis without hypercholesterinemia. Besides, there are instances cited in the literature when no correlation was observed experimentally between the development of hypercholesterinemia

and atherosclerosis. Some of these cases were mentioned earlier (the work of Adlersberg and his associates), and some of these will be cited later. Besides the cholesterin content of the serum, certain factors affecting the cholesterin deposit on the arterial walls are of considerable importance.

Table 1

Content of cholesterin of the serum in coronary atherosclerosis patients

Cholesterin (in mg percent)	Number of patients	
	absolute	percentage
122-150	37	8.2
151-180	68	15.1
181-200	90	20.0
201-250	186	41.3
251-300	55	12.2
301-350	11	2.5
351-390	3	0.7
Total	450	100

At present considerable significance is attached to the interrelation between various fractions of plasma lipoids. It is thought that phospholipids, lecithin in particular, aid in retaining non-water soluble cholesterin in a colloidal state; a fact which creates less favorable conditions for the deposit of cholesterin in arterial walls (A. I. Levin, 1934, B. V. Il'inskiy, 1940; Ahrens, Kunkel, Hueper, etc.). In this connection, considerable importance is attached to the ratio phospholipids/cholesterin in the blood serum (or inversely, cholesterin/phospholipids, as this index is customarily expressed abroad).

Gertler and his associates (1950) found that the ratio cholesterin/phospholipids in a group of patients

with coronary atherosclerosis was on the average higher than in the control group. However, the variations of this index, as well as the content of blood lipoids are very considerable. Therefore, the ratios of cholesterin/phospholipids in atherosclerotic patients and in healthy people in some cases overlap, a fact which we had mentioned earlier in regard to cholesterin.

We cosider it significant that upon a favorable change of the lipoid metabolism indices, under the effect of various substances which we used in our clinic on atherosclerotic patients, an increase in the ratio phospholipids/cholesterin was observed (P. Ye. Lukomskiy, V. I. Bobkova, L. A. Myasnikov, P. M. Savenkov, and others).

The problem of the correlation between various lipoid fractions of the serum is connected with the more general problem -- in what state are the lipoids circulating in the blood and what is the mechanism of their accumulation in the arterial walls? At present it is established that cholesterin does not circulate in the blood in a free state, but in the form of protein-lipoid complexes, or lipoproteins which Macheboeuf discovered for the first time 30 years ago (1929) in horse serum.

Lipoproteins are protein-lipoid complexes which consist of proteins, amino acids, and lipoids (cholesterin, phospholipids, and fatty acids). Lipoproteins in which the lipoids are bound with alpha-globulins are designated as alpha-lipoproteins, and lipoproteins where the lipoids are bound with beta-globulins are called beta-lipoproteins.

There are several methods of dividing lipoproteins into separate groups: ultracentrifugation (Gofman), paper electrophoresis, and chemical methods. At the present time the electrophoretic method is widely used in the clinic to separate the fractions of proteins and lipoproteins; it is a very accessible method and gives fairly accurate results for clinical purposes.

Both basic groups of lipoproteins differ in their physico-chemical properties -- an important fact in regard to atherogenesis. Lipoproteins are unstable compounds. However, one can distinguish the more solid from the less solid (less stable) lipoproteins. Alpha-lipoproteins are

more solid, beta-lipoproteins -- less solid and less stable.

Table 2

Composition and properties of lipoproteins of human plasma

Properties and composition	Fractions	
	alpha-lipoproteins	beta-lipoproteins
Molecular weight	0.2×10^6	1.3×10^6
Lipoids (in percentages)		
nonesterified cholesterin	3.3	8.3
cholesterin-esters	15.0	39.1
phospholipids	21.0	29.3
Total quantity of lipoids	39.3	76.7
Proteins	60.0	23.0

We cite some comparative data on the physico-chemical properties of alpha- and beta lipoproteins which Surgenor presented at the symposium on atherosclerosis, based on the studies of a number of authors (Table 2).

As is seen from Table 2, the molecular weight of beta-lipoproteins is many times greater than that of alpha-lipoproteins. Beta-lipoproteins contain more cholesterin than alpha-lipoproteins, while the quantity of phospholipids differs little in both fractions. Thus, the ratio phospholipids/cholesterin in beta-lipoproteins is much smaller than in alpha-lipoproteins.

Surgenor thinks that 28 percent of the total amount of serum cholesterin is contained in alpha-lipoproteins, and 63 percent -- in beta-lipoproteins. The cholesterin which is not bound with the basic fractions is distributed

among other protein fractions: gamma-globulins, the prothrombin-containing fraction, etc. According to other authors (Barr, Page, in healthy people 30 percent of the total cholesterin of the plasma is bound with alpha-lipoproteins, and 70 percent -- with beta-lipoproteins.

Lipoproteins, being unstable complexes, may disintegrate when penetrating the vascular wall and deposit the nonsoluble lipoids in it (N. V. Okunev, Page, and others). In this process the disintegration of beta-lipoproteins which have a high lipoid content and are less solid, takes place in the vascular wall more easily than that of alpha-lipoproteins. Therefore, beta-lipoproteins presumably play a larger role in atherogenesis than alpha-lipoproteins. The correctness of this point of view is corroborated by the fact that age as well as markedly pronounced ahterosclerosis (for instance, in individuals with the history of a myocardial infarct) increases the amount of total plasma cholesterin bound with beta-lipoproteins, while the one bound with alpha-lipoproteins is correspondingly reduced (Barr, 1953; Eder, 1954, and others).

Very indicative data on the effect of age are given by Barr in Table 3.

According to Eder, total cholesterin of the plasma of individuals who recovered from a myocardial infarct is, on the average, 274 mg percent; of these alpha-lipoprotein fractions contained only 13 percent of total cholesterin, and beta-lipoprotein fractions -- 87 percent. Analogous data are cited by Barr. Eder stresses the fact that in many patients with coronary atherosclerosis (who had recovered from a myocardial infarct) the cholesterin content of the serum was within normal limits, but its quantity corresponding to the alpha-lipoprotein fractions was lower, while the total quantity corresponding to beta-lipoprotein fractions showed an increase.

In recent years, in our clinic, the lipoprotein fractions were determined by the electrophoretic method in 200 patients with coronary atherosclerosis without expressed circulatory insufficiency. The beta-lipoprotein fraction in these patients represented, on the average, 83.5 percent

Table 3

Effect of sex and age on lipoids of human plasma of healthy individuals

Indicators	Women 18 to 35 years	Men 18 to 35 years	Women 45 to 65 years	Men 45 to 65 years
Total cholesterin, in mg percent	187.0	197.0	252.0	239.0
Phospholipoids, in mg percent	228.0	195.0	278.0	265.0
Ratio cholesterin/ phospholipoids	0.87	0.97	1.00	0.95
Percentage of total cholesterin in alpha-lipoproteins	34.3	25.2	23.4	22.9
Percentage of total cholesterin in beta-lipoproteins	61.8	72.0	75.0	75.3
Si 10 - 20	5.0	12,0	15.0	15.0

(i.e., was markedly increased) with variations from 61 to 97 percent; in only eight paties (four percent) was this fraction less than 70 percent, which we considered within normal limits. M. V. Bavina and M. Yu. Melikova found an increase in the beta-lipoprotein fraction in 48 out of 49 patients with coronary atherosclerosis.

Colman and associates studied the lipoprotein fractions by the method of ultracentrifugation and found in atherosclerosis an increase in Si fractions from 10 to 20, i.e., those fractions which correspond to beta-lipoproteins. Barr, having compared the basic indicators of lipoid metabolism (content of cholesterin in the plasma, ratio of cholesterin/phospholipids, amount of lipoproteins of class Si 10 - 20 and the distribution of the total quantity of cholesterin between alpha- and beta-lipoproteins) in patients with coronary atherosclerosis who had recovered from a myocardial infarct, concluded that the last indicator,

i.e., the increase of the share of total plasma cholesterin bound with beta-lipoproteins, had a more constant character.

The significance of definite lipoprotein fractions (beta-lipoproteins and Si 10 - 20 fractions) in atherogenesis is attested to by the fact that these fractions increased in those diseases which are generally considered to contribute to the development of atherosclerosis, -- diabetes mellitus, nephrosis, and certain other diseases (Barr, Eder, etc.). It is of interest also that there is a very small quantity of beta-lipoproteins and a large quantity of alpha-lipoproteins in the blood of animals which are, to a certain degree, resistant to atherosclerosis, e.g., dogs, cats, sheep, and rats. The content of phoapholipids as compared to cholesterin in dogs, for example, is higher than the quantity needed to keep it in solution (Page).

The importance which is at present attached to the changes in lipoprotein fractions in the pathogenesis of atherosclerosis has naturally raised the question of changes in protein-metabolism indices in this disease. These changes have been studied less than the indices of lipoid metabolism. In the experiments on animals (Fishberg, 1950; M. G. Kritsman, M. V. Bovina, 1953; T. N. Lovyagina, 1958) as well as in the clinic a reduction of a fraction of the albumins and an increase of globulins is observed upon the development of atherosclerosis. We observed a similar trend in the 200 patients with coronary atherosclerosis metnioned above, in whom lipoprotein fractions as well as protein fractions were determined (by the method of electrophoresis). The total quantity of blood proteins in these patients did not substantially differ from the norm.

The state of protein metabolism in atherosclerotic patients is of additional interest because there are indications in the literature of the possible protective role of full-value proteins upon the development of experimental atherosclerosis (Nishida, Brown, Lewis); lower content of full-value amino acids in the food contributes to the development of experimental atherosclerosis in monkeys (Mann, and associates). We must remember that proteins are

the initial material for such a powerful lipotropic factor as choline (L. A. Cherkes).

In speaking of the pathogenesis of atherosclerosis, we must mention briefly the connection between atherosclerosis and hypertension. The importance of increased arterail pressure as a contributing factor in the development of atherosclerosis is universally recognized. At the 14th All-Union Congress of Therapeutists, K. G. Volkova cited convincing data which showed that hypertension contributes to the development of atherosclerosis. This is also demonstrated by the development of atherosclerosis in the pulmonary artery system in hypertension of the pulmonary circle, and in the ascending aorta and its branches upon coarctation of the aorta, etc.

However, it would be incorrect to consider the connection between hypertension and atherosclerosis in its mechanical aspect only, i.e., in the fact that increased pressure within the arteries contributes to a more facile penetration of lipoids into their walls. Ye. M. Tareyev (1951) pointed out a certain similarity between hypertension and atherosclerosis and noted that atherosclerosis, like hypertnesion, is a cortico-visceral disease. He called attention to the change in the course of hypertension during the development of atherosclerosis when phenomena of coronary or cerebral atherosclerosis begin to emerge into the foreground, while the proper hypertension phenomena play a progressively smaller part in the clinical picture; even the level of arterial pressure may become lower, especially after a cerebral attack of a myocardial infarct. Ye. M. Tareyev warns against a simplified view of the interdependence between hypertension and atherosclerosis. At the First All-Union Congress of Therapeutists (1958), A. L. Myasnikov stressed the similarity of certain pathogenetic, biochemical, and other factors in hypertension and atherosclerosis and even raised the question on whether these two conditions are not a manifestation of the same disease which "in some cases appears as hypertension, and in others -- as atherosclerosis, and most frequently as both pathological processes simultaneously or consecutively." It is interesting to note that some pathologo-anatomists (A. M. Antonov) are inclined to

the opinion of the unity of these diseases.

It is necessary to mention that some foreign authors also think that the interrelation between hypertension and atherosclerosis is not determined by a purely mechanical factor. Thus, Schroeder is of the opinion that common basic factors exist in both diseases -- biochemical, geographical, etc. Thomas and Cohen point out the similarity of hereditary factors in hypertension and coronary atherosclerosis.

The foregoing data as well as daily clinical observations indicate that the close connection between hypertension and atherosclerosis is very complex, and is not, of course, limited only to the mechanical effect of an increased arterial pressure on the blood vessels. This connection must be viewed from the broader position of the pathogenesis of both diseases and their mutual effect on the course of the disease, when both conditions develop in the same individual.

The results of the study of the interrelation of these two diseases point out at the same time the role of the impairment of neural regulation of metabolic and vascular functions in the pathogenesis of atherosclerosis. Observations on the effect of neurotropic substances on the cholesterin level indicate indirectly the importance of neurogenic factors in the pathogenesis of atherosclerosis (T. D. Tisbekmakher, I. K. Shkhvatsabaya). In our clinic L. A. Myasnikov observed the beneficial effect of sedative preparation on the lipoid metabolism indices and the course of coronary atherosclerosis.

Of great importance in the study of atherosclerosis is the concept of N. N. Anichkov and his school on the phasic character of this disease, on the alternation of periods of progress of the disease with periods of abatement and even regression. The latter refers, of course, chiefly to the deposit of lipoids in the vascular walls.

In discussing the problems of prophylaxis and therapy of atherosclerosis we must dwell on the question of the importance of rational nutrition. The role of hypercholesterinemia in the pathogenesis of atherosclerosis, the possibility of inducing atherosclerosis by feeding cholesterin

to animals naturally led to the study of the importance of the alimentary factor in human atherosclerosis. Though experimental alimentary cholesterin atherosclerosis causes morphological vascular changes similar to human atherosclerosis, it cannot, nevertheless, be identified with human atherosclerosis in regard to pathogenesis. The alimentary factor in human beings does not play as important a role as in animals, and under normal conditions man does not receive such an excessive amount of cholesterin as experimental animals. At the same time, we must note that in the presence of an impaired metabolism -- a condition of the utmost importance in the pathogenesis of atherosclerosis -- the alimentary factor may acquire paramount importance. We must note that even experimental animals do not react equally to a cholesterin load; a fact apparently connected with individual metabolic characteristics (T. N. Lovyagin, T. A. Sinitsyna).

Under usual conditions the cholesterin level in human beings depends to a lesser degree on the exogenic cholesterin introduced with food than on the endogenic cholesterin formed in the organism, probably chiefly in the liver. An adult human being receives 400 - 500 mg of cholesterin with his food, and synthetizes about two gm (Page). An enhanced supply of food cholesterin reduces its endogen synthesis, while a reduced food intake of cholesterin is accompanied by its increased synthesis (Page). This, apparently, explains to a certain extent the failure of attempts at a substantial reduction of the cholesterin level by limiting the intake of food cholesterin. Keys (1956) found that changes in the intake of food cholesterin, within two-gm limits per day, does not substantially alter the cholesterin level. Since human food usually contains less than one gm of cholesterin, Keys feels that for practical purposes the variations in food cholesterin content have no important significance. Observations of a number of authors (Myasnikov, IL'inskiy, Keys and coworkers, Messinger) show that even considerable alimentary concentrations of cholesterin do not cause a substantially stable rise in cholesterinemia. According to observations of F. K. Men'shikov and V. P. Sokolovskiy, the prolonged

(40 to 45 days) administration of a diet "with a maximum limitation of food products containing cholesterin," did not lead to a substantial reduction of the plasma cholestrin level in patients with atherosclerosis; however, there was a somewhat different interrelation of cholesterin fractions present: the amount of cholesterin esters was lower, while that of free cholesterin was higher.

More definite data are available on the content of fats in the food and on their effect on lipoid and partial protein metabolism indices, as well as on coronary atherosclerosis morbidity. Numerous studies carried out in various countries enabled Keys and a number of other authors to come to the conclusion that atherosclerosis is much more frequent in countries where the population consumes a higher amount of animal fats with its food (United States, Great Britain, Denmark), while countries where the population consumes food with a lower caloric content of animal fats (Japan, Italy, etc.) show a lower incidence of atherosclerosis.

The importance of the character of nutrition, particularly of the fat content of food on atherosclerosis morbidity has also been demonstrated during the First and Second World Wars. Thus, Malmros showed that in countries where during World War II the consumption of fats, milk, and eggs was lower (Norway, Finland, Italy), the number of deaths due to atherosclerosis decreased.

In Leningrad, during the period of the blockade, the number of angina pectoris and myocardial infarct patients decreased, -- a fact directly connected with the lack of food and, particularly, with the lower intake of fats (D. M. Grotel'). K. G. Volkova found non-lipoid platelets in the coronary vessels of Leningrad residents who had suffered alimentary dystrophies and died of hypertension. The effect of fats consumed with food on the cholesterin level and development of atherosclerosis is explained by better absorption of cholesterin (exo- and endogenic) from the intestines. However, we must agree with Katz and Stamler that the problem is more complex and that we are dealing here with much more extensive metabolic disturbances. Despite the considerable evidence pointing to the apparent role of

excessive consumption of fats -- especially animal fats -- we must keep in mind, nevertheless, the great difficulties connected with the confirmation of this premise by epidemiological data. It is natural, that the thesis of Keys and his associates must be subjected to serious criticism (Yudkin, 1957, and others).

We cannot enter here into a detailed discussion. In our opinion, a correct practical approach to this problem is of substantial importance. Overestimation and underestimation of the importance of an excessive intake of fats are equally dangerous. The danger of overestimation lies in the fact that one frequently attaches exceptional importance to the alimentary factor in the etiology of atherosclerosis, while one undervalues or forgets the importance of other factors in its pathogenesis, the general pathological state of the organism even though it is connected with the predominant affection of certain vascular areas, the metabolic processes, functions of the cardio-vascular system, etc. Forgetting these general pathogenetic factors may often result in reducing all practical measures of the prophylaxis and treatment of atherosclerosis to the mere ordering of a corresponding nutrition schedule. On the other hand, underestimation of the alimentary factor, which with the background of impaired metabolism acquires a particularly important significance, leads to insufficient activity in the carrying out of one of the important and accessible therapeutic and prophylactic measures -- rational nutrition.

The unfavorable effect of an excessive intake of animal fats with food received convincing proof in connection with recent research which had been carried out to clarify the effect of various food fats on the lipoid metabolic indices. After Kinsell had demonstrated, in 1952, that animal fats increase cholesterinemia, while vegetable fats reduce it, a number of studies have been undertaken to determine the effect of various alimentary fats on the cholesterin content of the plasma. Ahrens investigated the effect of 25 different fats on the cholesterinemia level. The highest concentration of cholesterin in blood was observed upon the use of butter or cocoanut butter as the

sole fat ingreadient of food, the lowest -- upon the use of corn oil or safflower oil. It has been concluded that there is a correlation, expressed by an iodine number, between the unsaturated state of fatty acids which are contained in vegetable oils, and the rate of hypocholesterinemic action. Kinsell and associates (1958) came to the conclusion that linoleic acid, one of the three so-called noninterchangeable unsaturated fatty acids (linoleic, linolenic, and arachidonic), is the most active one in regard to the reduction of the cholesterinemia level. It is possible that arachidonic acid possesses an even more pronounced hypocholesterinemic property, but its content in animal fats is almost nil. The hypocholesterinemic action of unsaturated fatty acids was confirmed by the studies of a number of other authors (Bronte-Steward, 1956; Beveridge, 1956; Malmros and Wigand, 1957; Keys and associates, 1957, and others).

The hypocholesterinemic effect upon the use of unsaturated fatty acid preparations (Nothman, 1957 -- mixtures of linoleic, linolenic, and arachidonic acids, Kinsell and associates, Bronte-Stewart and associates, Malmros and Wigand -- ethyllinoleate) showed that noninterchangeable, unsaturated fatty acids are the active substances of vegetable oils responsible for the reduction of the plasma cholesterin level. The metabolism of these acids is closely bound with vitamins, about which we shall discuss later.

On 40 patients with coronary atherosclerosis with no evidence of circulatory insufficiency we used a mixture of ethyl esthers of fatty acids of linseed oil (the preparation -- linetol manufactured at our request by VNIKhFI) / All-Union Chemicopharmaceutical Scientific Research Institute /. The iodine number of linetol is 177.2. The administration of this preparation to patients for 20 days, at 20 ml per day, caused a statistically corroborated reduction of the plasma cholesterin content, beta-lipoproteins, and beta-globulins, and an increase in the albumin fraction. Our data demonstrate that non interchangeable, unsaturated fatty acids (linoleic and linolenic) exert a favorable effect on lipoid and protein metabolic indices.

The data cited above show that the use of large quan-

tities of fatty acids, butter in particular, exert an unfavorable influence on lipoid metabolic indices. In comparing it with the already mentioned "epidemiological" data, we must arrive at the very probable conclusion that an excessive content of animal fats in food (about 35 to 40 percent of the total caloric figure) exerts an unfavorable influence on the lipoid metabolism. Thus, the limiting of these fats in food is clearly indicated, with the replacement of a part of the fats by vegetable oils. In addition, it is important to keep in mind that upon hydrogeniation of vegetable oils saturation of the unsaturated fatty acids takes place and, as a result, vegetable oils lose their hypocholesterinemic properties.

One must consider the fact that excessive limitation of fats in food may have unfavorable sequels. Page, who tested on himself the effect of a prolonged, drastic reduction of fats in his diet, reports an adverse effect on his disposition; depression and increased irritability appeared, as well as gastro-intestinal distrubances, etc. There are indications in the literature than an excessive limitation in caloric intake and rapid loss of weight may place the organism, especially of fat people, in a situation analogous to the one which ensues following overfeeding with exogenically administered fats. Friedberg observed phenomenon of a myocardial infarct in fat people upon too rapid a loss of weight. Keys thinks that the diet in atherosclerosis must be limited in calories, of which fats will contribute about 25 percent of a 24-hour calorie-intake. Page calls attention to the danger of a diet in which fats cover less than 15 percent of a 24-hour calorie-intake. He points out correctly to the individual reaction of different people in regard to the effect of limitation of a 24-hour calorie-intake on the plasma content of cholesterin and lipoproteins. Plotz also feels that the human need for fats has not been determined precisely, and that fats must constitute no less than 15 percent of daily calorie-intake. Account must be taken of the fact that upon an insufficient content of fats in food, symptoms may appear which are connected with the lack of noninterchangeable unsaturated fatty acids. Bicknell and Prescott think that the "fat-insufficiency disease,"

described in rats by G. Burr and M. Burr, depends on the lack of these noninterchangeable, unsaturated fatty acids (linoleic, linolenic and arachidonic).

Another direction in which studies are carried out for finding therapeutic and prophylactic means in atherosclerosis is in the field of vitamins. Certain vitamins, e.g., Vitamin D_2, exert an unfavorable effect upon lipoid metabolic indices. Under the effect of this vitamin, the amount of plasma cholesterin of atherosclerosis patients increases as well as the accumulation of lipoids -- in the aorta of rabbits which had been given cholesterin (A. L. Myasnikov, M. V. Bavina). In contrast, ascorbic acid has a beneficial effect on lipoid metabolism in patients with atherosclerosis; it also inhibits the development of experimental cholesterin atherosclerosis in rabbits (I. A. Myasnikova, A. L. Myasnikov, L. A. Tyapina. Ye. P. Fedorova, etc.). Ascorbic acid is widely employed in the treatment of patients with atherosclerosis. The fear of thrombotic complications upon the administration of ascorbic acid proved to be exaggerated, as demonstrated by the works of N. A. Ratner and co-workers, A. V. Bukovskiy, and others).

The effect of vitamins of the B group on lipoid and protein metabolic indices is of considerable interest; some of these vitamins possess lipotropic properties. To these belong choline, Vitamin B_{12}, folic acid, pyridoxine. Choline is one of the most active lipotropic substances; therefore, its use in atherosclerosis is of considerable interest. The data in the literature on the effect of choline on lipoid metabolism indices in patients with atherosclerosis are contradictory. While a number of American authors (Katz, Stamler and associates) deny the importance of choline in the prevention of experimental atherosclerosis development and therapy of patients with atherosclerosis, other authors evaluate the choline effect as a positive influence (Yu. T. Pushkar', T. A. Sinitsyna, G. I. Koropova, Morrison and Rossi, Morrison and Gonzales).

Observations carried out in our clinic by P. M. Savenkov on 68 patients with coronary atherosclerosis showed that under the effect of choline a statistically definite reduction of the plasma content and an increase

in the content of phospholipids are observed, and the choline influences favorable the course of the disease.

Basing ourselves on the association of the physiological effect of choline, Vitamin B_{12}, and folic acid, we used also these vitamins in our clinic on patients with coronary atherosclerosis with favorable results (V. I. Bobkova). L. N. Ignatova observed the inhibiting effect of Vitamin B_{12} on the development of experimental cholesterin atherosclerosis of the aorta.

The effect of pyridoxine on lipoid metabolism indices is of considerable interest. Pyridoxine possesses lipotropic properties (Halliday, Peretti), has a direct relationship on the lipoid metabolism, especially that of the unsaturated fatty acids. Vitamin B_6 is essential in the desaturation of partially unsaturated fatty acids. Under its effect linoleic acid changes into arachidonic acid, and linolenic into hexenoic acid (Witten, Holman). The insufficiency of Vitamin B_6 in noninterchangeable, unsaturated fatty acids in rats gives a similar clinical picture, each of these factors substituting for the other to a certain extent (Schroeder).

Pyridoxine and unsaturated fatty acids enhance the lipotropic action of choline by mutually supplementing each other's action (Engel).

In experiments on monkeys Rinehart and Greenberg observed the development of atherosclerosis with insufficiency of pyridoxine in food. All these facts demonstrate that lack of pyridoxine may contribute to the development of atherosclerosis. Schroeder is of the opinion that the abnormal correlation between the saturated and unsaturated fatty acids in cholesterin esters (cholesterin esters are more easily soluble in unsaturated than in saturated fatty acids) may constitute an atherogenic factor upon the presence of a liminal content of pyridoxine in food, the latter phenomenon occurring in the United States in certain seasons. At the same time Schroeder attributes a certain significance also to the disturbance of the balance of trace elements, and bases his statement on the fact that the enzymic systems, in which B_6 enters as a co-enzyme, also contain a metal which activates them (Snell). Incidentally, it is

worth noting the growing interest in the possible role of trace elements in the pathogenesis of atherosclerosis and hypertension. There are experimental data on this problem. For instance, Curran and Costello (1956) observed in rabbits which had received cholesterin a marked reduction of cholesterinemia, inhibition of the endogenic synthesis of cholesterin, and its deposit in the aorta under the effect of vanadium. The hypocholesterinemic action of ethylendiaminotetra-acetate in humans is explained by Schroeder by the fact that this preparation binds the trace elements, zinc in particular, and contributes to their elimination with the urine. Since we cannot dwell in detail on this problem, we shall refer the reader to Schroeder's monograph in which considerable attention is devoted to the problem of the significance of trace elements.

The foregoing data on pyridoxine constitute a sufficient reason for attempts to employ it for therapeutic purposes in patients with atherosclerosis (Failey). In our clinic it was done by V. I. Bobkova on 35 patients with coronary atherosclerosis; large doses of pyridoxine (100 mg daily) administered for a period of 20 days led to favorable changes in the metabolic indices of lipoids and, partly, in proteins. S. D. Sheikh-Ali observed rabbits which had received large doses of cholesterin and pyridoxine, and he found a less pronounced cholesterinemia and lipoidosis of the aorta than in control animals.

As seen from the foregoing data, the effects of all the above-mentioned vitamins of group B, choline, Vitamin B_{12}, folic acid, pyridoxine, as well as the noninterchangeable, unsaturated fatty acids on the lipoid metabolism are closely interrelated. The physiological action of pyridoxine is also closely bound with the physiological action of another group B vitamin -- nicotinic acid. Pyridoxine participates in the transformation of tryptophan into niacin and in the methylation of the amide of nicotinic acid (S. M. Ryss).

The data in the literature on the effect of nicotinic acid on lipoid metabolism and atherogenesis are somewhat contradictory. I. A. Yakovleva found that nicotinic acid led to the enhancement of an experimental

cholesterin atherosclerosis in rabbits and a tendency to raise the cholesterin content of the plasma in patients with hypertension and atherosclerosis. But there are at present a number of works from abroad which show that large doses of nicotinic acid produce a considerable reduction in cholesterinemia level, and that nicotinic acid is therefore employed in large doses in the treatment of atherosclerosis patients (Altschul, 1955; Achor, 1958; Nava, 1958, and others).

As far as other vitamins are concerned, their effect on lipoid metabolism is expressed less clearly. Vitamin B_1 has no substantial effect on the development of experimental atherosclerosis and cholesterinemia level in patients with atherosclerosis (A. L. Myasnikov). Data on the effect of A_6 and E on lipoid metabolism and development of atherosclerosis are somewhat contradictory (see literature: N. V. Okunev).

Besides lipotropic substances which belong to the vitamins of the B group, methionine, lecithin, and lipocain were also used for therapeutic purposes in atherosclerosis. Hueper (1949) considered, for theoretical reasons, that it is expedient to use lecithin of vegetable origin (from soya beans) for the treatment of atherosclerosis. The molecule of lecithin contains choline, -- a fact which apparently determines the lipotropic properties of lecithin; these properties manifest themselves when depancreatinized dogs receive fresh pancreatic tissue or even plain lecithin. Another lipotropic substance of the pancreas is lipocain (S. M. Leytes), or the lipocaic of foreign authors. The data on its effect on lipoid metabolism indices are somewhat contradictory. Thus, Huber, Brown, and Casey (1937) observed that rabbits which had received cholesterin showed a retardation of the development of hypercholesterinemia and atherosclerosis under the effect of lipocain. At the same time, Vermeulen, and Dragstedt (1942) could not confirm it, although they point out that it was possible due to the insufficient dosage of lipocain or the inadequate method of its administration. Z. A. Bondar' and co-workers observed that patients with Botkin disease who received lipocain showed an increase

in the amount of phospholipids of the plasma. Certain foreign authors noted an increase of alpha-lipoproteins in patients.

Lecithin and lipocain were employed for therapeutic purposes in patients with atherosclerosis. A. A. Kleonina observed that patients with atherosclerosis and hypertension who had received lecithin showed slight changes in cholesterinemia and a more substantial increase in the plasma lecithin. P. M. Savenkov, in our clinic, used lipocain on 40 patients with coronary atherosclerosis and observed that a predominant majority showed a considerable increase of plasma phospholipids, and a corresponding increase of the phospholipid cholesterin ratio. The effect on cholesterinemia was insignificant.

Of the other substances possessing lipotropic properties we shall mention methionine. Its lipotropic properties are probably connected with the fact that methionine with its mobile methyl groups participates in the endogenic synthesis of choline (du Vigneaud). Methionine was used in our clinic (Van Pu) on 45 patients with coronary atherosclerosis. In the majority of cases favorable changes were noted in the metabolic indices of lipoids and, partly, in proteins. The effect of methionine on the phospholipid level in the plasma was more pronounced than its effect on cholesterinemia. G. I. Koropova observed similar changes of certain lipoid metabolism indices upon prolonged use of methionine.

The foregoing data on the importance of the consumption of fats, unsaturated fatty acids, vitamins, and lipotropic substances on the origin of atherosclerosis must be taken into consideration when one formulates a rational diet. The absorption of cholesterin in the intestines and its elimination with excrement must also be considered. Not only food cholesterin is absorbed in the intestines, but also a considerable part of the endogenous cholesterin which is secreted into the intestinal canal together with bile. Attempts were made to reduce cholesterinemia by the employment of substances which inhibit absorption of cholesterin in the intestines and stimulate its elimination with the excrements. Of these substances the effect of vegetable

sterols, the so-called phytosterols, has been most satisfactorily studied. There are clinical observations and experimental data which indicate that the administration of beta-phytosterol causes a reduction in the cholesterin content of the blood (Peterson, Pollak).

We think that the foregoing data may serve as a basis for working out a nutritional regimen directed toward the prevention of the development and progress of atherosclerosis. The basic theses are reduced to the fact that nutrition must not be excessive, particularly in regard to animal fats; it is expedient to replace a part of animal fats by vegetable fats containing a large amount of unsaturated fatty acids. The food must contain a sufficient quantity of full-value proteins, lipotropic substances, and vitamins which would exert a favorable effect on the lipoid and protein metabolism. It must also contain a sufficient quantity of vegetable cellulose and other substances which would ensure a regular intestinal evacuation. We do not consider the question of the salt content of food: first, it does not follow from the context of problems which have been discussed, and second, it is to a great extent determined not by the atherosclerotic process as such, but by its concrete clinical manifestations (myocardial infarct, atherosclerotic cardiosclerosis with circulatory insufficiency, etc.).

We are discussing here only the general principles of a nutritional regimen without attempting to suggest definite schedules and diets, which is not our aim. The description of definite schedules and diets in atherosclerosis can be found in a number of works of Soviet and foreign authors (B. V. Il'inskiy, F. K. Men'shikov, V. P. Sokolovskiy, Luisada, Rinzler, and others).

In the pathogenesis of atherosclerosis a definite role is played by endocrine factors. It is a universally known fact that the incidence of coronary atherosclerosis and myocardial infarct morbidity is higher in men than in women. However, in the more advanced stage of life this difference is less pronounced. Table 3 shows data on the effect of sex and age on lipoid metabolism indices. In young men the average figures of total plasma cholesterin

and its percentage of beta-lipoproteins are higher than in women. These ratios change at a more advanced age. Some workers consider it one of the causes of an earlier onset of atherosclerosis in men than in women. One cannot overlook the effect of endocrine factors in the lower incidence of coronary atherosclerosis in women before the menopause, and in the marked increase of morbidity in women after the onset of the menopause.

The data in the literature on the effect of male and female sex hormones on the development of experimental cholesterin atherosclerosis, as well as clinical observations on the use of sex hormones for therapeutic purposes in coronary atherosclerosis are somewhat contradictory. We cannot discuss in detail the experimental data and shall limit ourselves to the statement that the estrogenic hormone inhibits the development of experimental cholesterin atherosclerosis in cockerels (Pick, Stamler). Castration leads to an enhancement of cholesterin atherosclerosis in rabbits (Shapiro, Kh. Kh. Mansurov).

Barr, Eder, and Robinson observed very favorable changes in the lipoid metabolism indices, reduction of cholesterinemia, increase of the ratio of total cholesterin of the alpha-lipoproteins, and a reduction of the ratio of cholesterin/phospholipids in men with coronary atherosclerosis after they had been treated with estrogenic hormones. The use of methyltestosterone caused changes of these indices in the opposite direction. Kh. Kh. Mansurov, however, observed reduction of cholesterinemia following the use of this androgenic hormone. The problem of the possible therapeutic use of sex hormones in coronary atherosclerosis requires further careful study, particularly in view of the fact that upon protracted and effective treatment of men, who had suffered a myocardial infarct, with estrogenic hormones, disturbances of their sexual function have been observed (Barr, Robinson and associates).

The connection between diabetes and the development of atherosclerosis has been known for a long time. In the USSR the incidence of diabetes is much lower than in some foreign countries, e.g., the United States. According to the American authors, coronary atherosclerosis, closing of

the lumen of coronary arteries, and myocardial infarct are found much more frequently in autopsies of diabetic patients than in those who had no diabetic history (Enklewitz, 1934; Root, 1939; Stearns, Schlesinger, 1947; Feldman and Feldman, 1954, and others). In diabetic patients atherosclerosis develops at an earlier age, and the usual difference of coronary atherosclerosis and myocardial infarct incidence between men and women is levelled out. The latter, presumably, depends on the fact that myocardial infarct develops more frequently in woemn diabetics than in men. Thus, according to Wright, of 774 men ill with myocardial infarct only 7.1 percent were diabetics, while among 240 women with myocardial infarct, 24.2 percent were diabetics. Analogous figures were cited by a number of other authors. These facts raise the problem of the connection of the pancreas with atherosclerosis, a problem which in spite of experimental studies (for literature see Katz and Stamler), cannot at present be considered completely clarified.

Definite data are available on the effect of the thyroid on lipoid metabolism and the development of atherosclerosis. It was demonstrated experimentally that the thyroid hormone inhibits the development (I. V. Friedland, 1933) and accelerates resorption (V. V. Tatrskiy and V. D. Tsinzerling, 1950) of the lipoidosis of the aorta in rabbits which had been fed cholesterin. Methylthiouracil is used on dogs to inhibit the function of the thyroid, while they are fed cholesterin to induce atherosclerosis. It is known that myxedema is accompanied by hypercholesterinemia.

The use of thyroid preparations for therapeutic and prophylactic purposes did not find much application, for thyroxine itself is not harmless to the cardiovascular system. There is evidence that, under the effect of the thyroid hormone, the content of catecholamines (adrenalin, noradrenalin) in the myocardium increases. These increase the use of oxygen by the myocardium and thus reduce the coefficient of its useful action. This leads to the development of myocardial anoxia, especially in patients with coronary atherosclerotic arteries; these arteries are unable to dilate adequately and thus to increase the blood supply to the heart muscle and compensate for the enhanced

consumption of oxygen by the myocardium (Raab). Nevertheless, some attempts were made to treat patients having atheroxlerosis with iodothyrin (N. I. Pekarskiy, 1956).

The problem of the effect of ACTH and cortisone on lipoid metabolism is very important. The necessity arises, at times, to use these preparations on patients who, besides having a disease in which hormonal therapy is indicated, also show manifestations of atherosclerosis. In recent years the hormones of the adrenal cortex have been employed in the treatment of patients with myocardial infarct and those with an inadequate blood circulation (Pendl, and others). The experimental data on the effect of ACTH and cortisone on lipoid metabolism are contradictory. Stumpf and Wilens administered cortisone to rabbits who had been receiving cholesterin, and observed its inhibiting effect on the development of atherosclerosis. Such an effect was not corroborated by Cook though he observed somewhat attenuated manifestions of hypercholesterinemia and atherosclerosis upon administration of ACTH. Stamler, Pick, and Katz fed cortisone and cholesterin to chicks and observed a more marked development of atherosclerosis of the aorta and coronary arteries than in chicks which had received only cholesterin; cortisone had no effect at all on hypercholesterinemia, phospholipemia, and the cholesterin/phospolipid ration. Administration of ACTH did not enhance atherosclerosis but increased hypercholesterinemia. We have already cited the data by Adlersberg and associates on the effect of steroid hormones of the adrenal cortex and ACTH on experimental atherosclerosis in rabbits.

Data in the literature on changes in the lipoid metabolism indices in patients who had received ACTH and cortisone are scanty and also somewhat contradictory. In this connection, our clinic investigated the indices of the metabolism of lipoids, lipoproteins, and proteins on 50 patients suffering from rheumatoid polyarthritis, rheumatism, and bronchial asthma who had received hormonal therapy (V. F. Zaytsev). In the majority of these cases treatment with hormones was accompanied by a reduction of the cholesterin content, increase of plasma phospholipids, reduction of beta-lipoproteins, increase of albumins, and

reduction of blobulins in the plasma. On the basis of these results, we consider it possible to use ACTH and cortisone when so indicated, even if the patients show certain manifestations of atherosclerosis. It is understood, of course, that this problem requires further study.

As seen from the cited data, the role of endocrine factors in the pathogenesis of atherosclerosis and of the use of endocrine preparations for prophylactic and therapeutic purposes is still not clear and requires further investigation.

In discussing the problem of treatment of patients with atherosclerosis we must also mention the effect of heparin on lipoid metabolism indices. Hahn (1943) observed that the intravenous administration of heparin in dogs with alimentary lipemia causes a clearing-up of the blood plasma. Further studies showed that this "clearing-up factor" is a lipoprotein lipase which catalyzes the hydrolysis of triglycerides of lipoproteins into fatty acids and glycerin (Korn). Lyon, Jones, Gofman and associates (1951) demonstrated that under the effect of heparin a favorable change of blood lipoproteins takes place in patients with atherosclerosis, as well as in experimental rabbits which have been receiving cholesterin. In the latter, heparin exerted an inhibiting effect on the development of atherosclerosis. Stamler and Katz stress the fact that these changes in the lipoprotein fractions were not accompanied by substantial changes in the general plasma cholesterin level, nevertheless they exerted an inhibiting action in atherosclerosis development. Nikkila also observed that under the action of heparin there had been an increase of alpha- and a reduction of beta-lipoprotein fractions.

We cannot dwell on the problem of the mechanism of the action of heparin, which is still obscure (for literature see N. V. Okunev, Stamler and Katz, Korn). We shall note only that attempts have been made to use heparin in patients with atherosclerosis in order to alleviate the lipoid metabolism (Graham, Lyon, Gofman and associates, A. L. Myasnikov, N. A. Ratner and associates, Engelberg and associates). It is still premature to speculate on whether

heparin will be accepted in practice for the treatment of coronary atherosclerosis (we do not speak, of course, of its use as an anticoagulant).

As seen from the foregoing data, the problems of the pathogenesis, treatment, and prophylaxis of atherosclerosis are undergoing a thorough study at present in clinics as well as experimentally. Special attention is concentrated on the problems of metabolic disturbances in atherosclerosis, not only of lipoids but proteins and lipoproteins as well. There is no doubt that the problems of pathogenesis of atherosclerosis will in the future undergo studies on a broader front, since it is a known fact that at the base of atherosclerosis lie disturbances of metabolic regulation and, probably, of many other functions of systems and organs, of which the foremost is the cardio-vascular system. Up to the present time the studies were concentrated chiefly on the search for effective measures for the prophylaxis and treatment of atherosclerosis. So far, no definitive achievements have been obtained in this field. However, certain trends have been mapped out in the development of the problem of prophylaxis and therapy of this disease which offer some promise. To these trends belongs the study of the problem of nutrition. Substantial, but not definitive, data have been obtained in regard to the vitamins, lipotropic substances, and hormones on metabolism and on the development of atherosclerosis. The question of the significance of endocrine factors in the pathogenesis of atherosclerosis requires further study. Hormone therapy has not as yet received widespread use. This problem too, requires further study. Alongside the enumerated factors are many others which were not the subject of discussion in this article, e.g., the regimen of work and home life, physical training, therapeutic exercises, physical activity in the wider sense of the word.

Of considerable importance is the change in our views on the evolution of atherosclerosis. At the present time the idea of atherosclerosis as the inevitable companion of old age, as a disease of an unyielding progressive character leading to a fatal exit, is gradually giving place to a more optimistic view. A certain phasic character was

observed in the course of this disease; periods of progress may, apparently, alternate with periods of abatement and even partial retrogression. Such a concept of the course of this process stimulates physicians' thoughts toward a search for effective means of prevention and treatment of atherosclerosis, a search which no doubt will eventually be crowned with success.

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